REMARKS/ARGUMENTS

Claims 1–20 are pending in the captioned application. Applicant has cancelled claims 13–14, without prejudice.

The Examiner has objected to claim 13 under 37 C.F.R. § 1.75(c) as "as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 is recited as a independent product claim that should be written in independent form".

In response to the Examiner's objections, Applicant has cancelled claim 13, without prejudice. Applicant respectfully asserts that this overcomes the Examiner's objections which should be withdrawn.

The Examiner has rejected claims 1–11 and 13–20 under the judicially created doctrine of obviousness-type double patenting as "being unpatentable over claims 1, 6-15, 20-22, 25, 28 and 29, of copending Application No. 10/478,910 in view of Maggio et al (Enzyme-lmmunoassay, Department of Pathology, Scripps Clinic and Research Foundation, May 14, 1987)".

The Examiner states, "The claims are drawn to a method of derivatizating the N-terminus or N-termini of one or more polypeptide or peptides with at least one acidic reagent containing a sulfonyl or sulfonic acid moiety coupled to an activated ester moiety to provide one or more peptide derivatives. The copending application only differs from

the instant claims in not teaching that the peptide or polypeptide is immobilized to a solid support at least during step (a)".

The Examiner further continues, "...Maggio et al discloses that the advantage of a solid phase assay format is that washing can be carried out very easily by immersion and if microplates are used, they can be very convenient to wash thereby reducing labor in performing the assay...It would have been obvious to one of ordinary skill in the art to modify the claimed method to include the use of a solid support because wash steps can be carried out easily thereby reducing labor in performing the assay. Further, performing solid phase assays are well known in the art".

In response, Applicant wishes to inform the Examiner that patent application serial number 10/478,910 has been abandoned.

Applicant respectfully asserts that the Examiner's rejection has been overcome and should be withdrawn.

The Examiner has rejected claims 1–6, 10–13 and 15–18 under 35 U.S.C. § 102(a) as "being anticipated by Keough et al (WO 00/43792)". Specifically, the Examiner states, "Keough et al anticipates the instant invention by teaching a method of identifying a polypeptide by derivatizing the N-termini of one or more peptides with one or more acidic moieties having a pKas of less than about 2 when coupled with the polypeptide or peptide to provide one or more derivatized analytes. This method is analyzed by mass spectrometric techniques to provide a fragmentation pattern (summary)".

The Examiner continues, "the fragmentation pattern of the peptide is interpreted to sequence the polypeptide (page 7, lines 1-2). Thomas et al discloses coupling an acidic moiety reagent to the N-terminus of a cysteine-containing peptide, followed by oxidation to produce peptides containing two acidic moieties (sulfonic acids). The preferred acidic moieties are 2-sulfoacetyl, 2-sulfobenzoyl and 3-sulfopropionyl moieties (page 9, lines 1-15). These preferred acidic moieties are sulfonyls coupled to an ester moiety such as sulfosuccinic anhydride, and 2-sulfobenzoic acid cyclic anhydride and others (page 9, lines 1-30)."

The Examiner concedes, "Keough et al is silent with respect to the half-life of the acid reagent not being less than 10 minutes, however, it is the Examiner's position that this teaching is inherent to what the instant reference teaches. Keough et al teaches the acid reagents utilized in the instant invention, therefore these reagents will inherently exhibit a half-life in aqueous solution of not less than 10 minutes".

In response, Applicant respectfully reiterates the arguments presented in the previous response to this rejection, and points out that claim 1 recites that the acidic reagent contains "a sulfonyl moiety coupled to an ester moiety"; such is neither taught, nor even suggested, by the Keough, et al. reference. While Applicant concedes that Keough, et al. does teach coupling of sulfonyls to anhydride reagents, anhydrides are not esters. The benefits of use of the reagents of the instant invention are disclosed at pages 8–11 of the captioned application, and include aqueous stability. Indeed, as stated at page 9, lines 5–11, one of the advantages of the instant invention compared to the

disclosure of the Keough, et al. reference "resides in the fact that according to the present invention all steps can be carried out under aqueous conditions. As previously suggested technology required to dry-down steps and several small pH changes from basic to acidic, and vice versa, the present method is much more amenable to automation".

In response to this argument, the Examiner states, "although the anhydride reagents recited by Keough are not esters; a sulfonyl group coupled to an ester is found within the 3-sulfopropionic anhydride structures, (see example 8, page 14) and as evidenced by applicant's instant specification on page 23 which describes the synthesis of a NHS ester from a 3-sulfopropianic anhydride. Although the reference of Keough et al did not synthesize an NHS ester from 3-sulfopropionic anhydride, it is apparent that an ester coupled to a sulfonyl group is within the structure of the 3-sulfopropionic anhydride. The instant claim 1 calls for at least one acidic reagent containing a sulfonyl moiety coupled to an ester moiety, therefore, Keough satisfies the limitation of claim 1".

In response, Applicant fails to understand the Examiner's statement. Specifically, the compound disclosed at page 14, example 8 of the Keough, et al. reference is 3-sulfopropionic anhydride. Even if applicant were to accept the Examiner's contention that this compound embodies "a reagent containing a sulfonyl moiety coupled to an ester moiety", which Applicant does not concede, anhydrides are very sensitive to water and would not exhibit the half-life recited in the claim "a half-life in aqueous solution of not less than 10 minutes at room temperature". Indeed, as stated at page 24, lines 23–25 of the captioned application, 3-sulfopropionic anhydride "was very sensitive to water and it

was necessary to dry all equipment in an oven before use and to do the reaction and purification under an argon atmosphere".

Further, at page 3, lines 5–10 of the captioned application, it is stated that one objective of the instant invention is achieved by "using a novel class of water-stable derivatization reagents, which comprise a sulfonyl moiety coupled to an activated acid moiety". Thus, the water stability recited in the claim is an inherent characteristic of the reagents used in the methodology of the instant invention.

Such water stability is neither disclosed nor even suggested by the Keough, et al. reference.

As for the Examiner's statement regarding Applicant's assertion that all the steps can be carried out under aqueous conditions making it amenable to automation, versus the previous technology which requires dry-down steps. This assertion is noted but not found persuasive because these benefits are not found in the claims", Applicant respectfully directs the Examiner's attention to the statement in claim 1(a), which states that the reagent exhibits "a half-life in aqueous solution..." Such benefits are clearly a result of this stability in aqueous solution.

In view of the foregoing, Applicant respectfully asserts the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 13–14 under 35 U.S.C. § 102(e) as "being anticipated by Little et al (USP6,322,970)". Specifically, the Examine states, "Little et al anticipates the instant reference by teaching reagents comprising a sulfonyl moiety

coupled to an ester moiety and a reagent selected from the group consisting of 3-sulfopropionic N-hydroxysuccinimide esters (column 59, lines 65-67)".

In response, Applicant respectfully asserts that the Examiner is mischaracterizing the reference. Specifically, the cited passage of Little, et al. discloses a linker which is suitable for attaching a peptide to a solid support in the "activated carboxy form such as sulfo-NHS ester". However, there is no disclosure, nor even any suggestion, of a reagent which can be utilized in a method of identifying a polypeptide (claim 13) or suitable for use in peptide derivatization in an aqueous solution (claim 14) as recited in the claims. Accordingly, Applicant respectfully asserts that the Examiner's rejections cannot be sustained and should be withdrawn.

In response to these arguments, the Examiner states, "the examiner views claims 13-14 as independent claims reciting a reagent. Claims reciting a reagent are considered to be product claims. Product claims are not given patentable weight for intended use. The reference of Little et al recites the instant reagents of claims 13-14 and therefore satisfies the limitations of the instant claims. Further, claim 13 appears to depend from a method claim, however, it is claimed as a product, which does not further limit[ed] the claimed method (see above objection). Claim 13 has also been rejected as an independent product under 102 and as part of a method claim under 103".

In response, Applicant has cancelled claims 13 and 14, without prejudice.

The Examiner has rejected claims 7–9 and 19 under 35 U.S.C. § 103(a) as "being unpatentable over Keough et al in view of Little et al (USP#6,322,970)". Specifically, the Examiner states, "the teachings of Keough et al are set forth above and differ from the instant claims by not disclosing a sulfonyl group being coupled to a particular ester such as N-hyroxysuccinimide (NHS) ester".

The Examiner continues, "Little et al discloses a process for determining the identity of a target polypeptide using mass spectroscopy (abstract). Little et al discloses that target polypeptides can be captured by conjugation to a solid support by immobilizing. The conjugation can be mediated through a linker such as a sulfo-N-hydroxysuccinimide (NHS) ester that facilitates conjugation of the polypeptide through it amino terminus..." The Examiner further states, "claim 12 recites a step of protecting lysine residues prior to derivatizing. Little et al discloses that the termini of a target polypeptide are more reactive than the amino acid side groups and therefore the amino acid residues should be blocked prior to performing the reaction of interest (column 60, lines 27-50)".

The Examiner concludes, "it would have been obvious to one of ordinary skill in the art to modify the reference of Keough et al to couple an N-hydroxysuccinimide (NHS) ester to a sulfonyl group taught by Little et al to facilitate conjugation of peptides to a solid support which has the advantage of being manipulated so that reagents and undesirable reaction products can be washed from the remaining immobilized

polypeptide, which can then be cleaved from the solid support and analyzed by mass spectrometry (column 60, lines 17-27)".

In response, Applicant respectfully points out that the Little, et al. reference discloses the utilization of NHS esters to facilitate attachment to a solid support. As stated at column 4, lines 38–52, this immobilization provides "a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypeptide prior to mass spectrometry". Such is quite different from the instant invention wherein the derivatization is done in aqueous solution and does not require attachment to a solid support. The benefits of such aqueous solution derivatization are discussed above, and are neither disclosed nor even suggested by either the Keough, et al. or Little, et al. references.

In response, the Examiner has stated, "Applicant['s] argument that the references of Keough et al and Little et al does not disclose or suggest derivatization of the peptides in aqueous solution. This argument is noted but not found to be persuasive".

The Examiner continues, "In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Keough et al teaches derivatization in an aqueous solution, which are called for by the instant claim 1 (see page 5, lines 11-12). The reference of Little et al was relied on for its teaching of a particular (NHS) ester group,

which discloses that (NHS) esters facilitate conjugation of the polypeptide to a solid support during the method of derivatization of the polypeptide through its amino or carboxyl terminus. Although applicant contends that the instant invention is different from the prior art of Keough et al and Little et al, these differences do not appear in the claims. Therefore, it appears to the examiner that the combination of the references is proper".

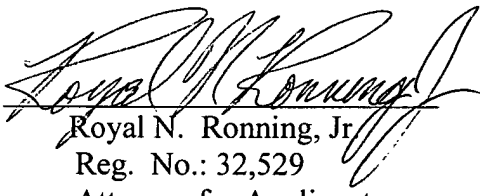
In response, Applicant reiterates that the references, alone or in combination with one another, neither disclose nor even suggest derivatizing polypeptides in aqueous solution, nor do they disclose or even suggest that the reagents for derivatization exhibit a half-life in aqueous solution of not less than 10 minutes at room temperature. This is clearly recited in claim 1 (upon which claims 7–9 are dependent) and claim 15 (upon which claim 19 is dependent). Thus, Applicant respectfully asserts the differences between the instant invention and the prior art of Keough, et al. and Little, et al. do appear in the claims.

In view of the foregoing, Applicant respectfully asserts the Examiner's rejections cannot be sustained and should be withdrawn.

In view of the foregoing, Applicant respectfully asserts the Examiner's rejections cannot be sustained and should be withdrawn. Applicant believes that the claims, as amended, are in allowable form and earnestly solicit the allowance of claims 1–12 and 15–20.

Respectfully submitted,

AMERSHAM BIOSCIENCES CORP

By: 
Royal N. Ronning, Jr.
Reg. No.: 32,529
Attorney for Applicant

Amersham Biosciences Corp
800 Centennial Avenue
P. O. Box 1327
Piscataway, New Jersey 08855-1327

Tel: (732) 457-8423
Fax: (732) 457-8463

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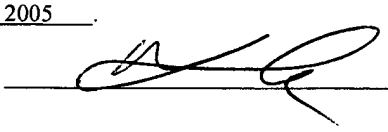
Signature: 

Name: Melissa Leck